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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

10/524399

Applicant's or agent's file reference 4-32608A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/09292	International filing date *(day/month/year)* 21.08.2003	Priority date *(day/month/year)* 22.08.2002
International Patent Classification (IPC) or both national classification and IPC C12Q1/68		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.02.2004	07.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Botz, J Telephone No. +31 70 340-4513

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/09292

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-23 as originally filed

Claims, Numbers

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-4 (industrial applicability), 3-6,8,9 (completely), 1-14 (partially)

   because:

   ☒ the said international application, or the said claims Nos. 1-14(partially) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 3-6,8,9 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☒ the claims, or said claims Nos. 3-6,8,9 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-14(partially),1-4(industrial applicability)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	12-14
	No:	Claims	1,2,6,10,11;
Inventive step (IS)	Yes:	Claims	12-14
	No:	Claims	1,2,6,10,11;
Industrial applicability (IA)	Yes:	Claims	5-14
	No:	Claims	1-4

2. Citations and explanations

   see separate sheet

III. Non-establishment of opinion (Continuation)

1. The applicant is reminded that claims or parts thereof for which no International Search Report has been established, will not be the subject of the International Preliminary Examination (**Rules 66 (1) (e); 70 (2) (d) PCT**). The conclusions drawn in the International search report are briefly summarized below: the **ISA** has found a non-compliance with **Article 13.1 PCT**, unity of invention. **Claims 1 - 14** have only been searched partially, namely with respect to the first invention, the latter being considered for the subsequent examination procedure.

2. **Claims 1 - 4** relate to subject-matter considered by the **IPEA** to be covered by the provisions of **Rule 67.1 (iv) PCT**. Consequently, no opinion is formulated with respect to the industrial applicability of the subject-matter of these claims (**Article 34(4)(a)(i) PCT**).

3. The terms "pre-administration sample" and "post-administration sample" in **claim 3** are no generally used terms, and could lead to misunderstanding by the skilled in the art. Said terms must be defined more clearly, e.g. in a technical manner. In addition, **claim 3** is not supported by the description as required by **Article 6 PCT**: in particular the **IPEA** cannot find any evidence for step (f) of claim 3, which encompasses as the last step of said method, namely the adjusting of the agent. Said claim is therefore exempt from further examination.

4. The method of **claim 4** is not supported by the description, since no such method is detailed in the description. The description simply reformulates the problem of establishing such a method for preventing, inhibiting, reducing or treating CR in a transplanted subject, **Article 6 PCT**. No examination can be carried out on said claim.

5. **Claim 5** is not clear, since it is not revealed how the method properly works. In other words, it is not revealed how to get from the monitoring of mRNA expression levels of one or more genes or gene products to the identification of agents for use in the prevention, inhibition, reduction or treatment of CR. The applicant does not sufficiently identify the technical features / methodological steps of the method claimed but merely reformulates the underlying technical problem. **Claim 5** is formulated as an effect to be achieved and therefore does not meet the requirements of **Article 6 PCT** in that the matter for which protection is sought is not clearly defined. No examination can be carried out on said claim.

6. **Claims 8** and **9** are not supported by the description since the description only provides support for the performance of the underlying methodology with mRNA-transcripts and not with protein (**Article 6 PCT**).

V. Reasoned statement (Continuation)

1. CITATIONS

Reference is made to the following documents:

D1: SUTHANTHIRAN M: "Human renal allograft rejection: molecular characterization." NEPHROLOGY, DIALYSIS, TRANSPLANTATION: OFFICIAL PUBLICATION OF THE EUROPEAN DIALYSIS AND TRANSPLANT ASSOCIATION - EUROPEAN RENAL ASSOCIATION. ENGLAND 1998, vol. 13 Suppl 1, 1998, pages 21-24, XP002267088 ISSN: 0931-0509

D2: SHARMA V K ET AL: "Molecular correlates of human renal allograft rejection" TRANSPLANTATION PROCEEDINGS, vol. 30, no. 5, August 1998 (1998-08), pages 2364-2366, XP002267089 Meeting on New Dimensions in Transplantation: Weaving the Future;Florence, Italy; February 16-19, 1998 ISSN: 0041-1345

2. NOVELTY (Art. 33(2) PCT)

1. **D1** discloses the provision of a molecular transcriptional profile by means of RT-PCR, identifying the transcript of TGF beta as significantly up-regulated in the rejection process of human renal allografts (also called intragraft gene expression), care especially for table 1. TGF beta is thereby identified to be positively correlated with chronic renal rejection. This is confirmed by the finding that amongst those patients that showed no signs / clinical indication for CR, most were negative for TGF beta expression.
2. Prior art **D1** is novelty destroying to **claims 1, 2, 6, 10** and **11**.

3. **D2** also discloses molecular correlates of human renal allograft rejection by obtaining 102 renal allografts from 107 patients and analyzing these

samples for intragraft RNA expression by means of RT-PCR, c.f. table 2.

4. Prior art **D2** is novelty destroying to **claims 1, 2, 6, 10** and **11**.

5. The present application does not satisfy the criterion set forth in **Article 33(2) PCT** because the subject-matter of **claims 1, 2, 6, 10** and **11** is not new in respect of prior art as defined in the regulations (**Rule 64(1)-(3) PCT**).

3. INVENTIVE STEP (Art. 33(3) PCT)

1. In case the applicant would overcome above mentioned objections with respect to **Article 6 PCT** and **Article 33(2) PCT** the IPEA would follow the following inventive step reasoning (**Art. 33(3) PCT**) for **claims 1, 2, 6, 7** and **10 - 14**.

2. Document **D1** is considered to represent the most relevant state of the art for **claims 1, 2, 6, 7** and **10 - 14** and discloses the provision of a molecular transcriptional profile by means of RT-PCR, identifying the transcript of TGF beta as significantly up-regulated in the rejection process of human renal allografts (also called intragraft gene expression), care especially for table 1. TGF beta is thereby identified to be positively correlated with chronic renal rejection. This is confirmed by the finding that amongst those patients that showed no signs / clinical indication for CR, most were negative for TGF beta expression.

3. The subject-matter of **claims 1, 2, 6, 7** and **10 - 14 differs** in that the gene for cytokeratin 15, namely KRT15 has been identified as biomarker for renal transplant rejection.

4. The **problem to be solved** by the subject matter of **claims 1, 2, 6, 7** and **10 - 14** may therefore be regarded as the identification of alternative biomarkers for renal transplant rejection.

5. The **solution** would be the identification of the gene for cytokeratin 15, namely KRT15 as biomarker for renal transplant rejection.

6. This solution can be considered as involving an inventive step (**Article 33(3) PCT**) since there is no indication in the prior art identifying the gene for cytokeratin 15, namely KRT15 as biomarker for renal transplant rejection. The is no second prior art that, if combined with the teaching of closest prior art **D1**, would make the skilled in the art come up with the solution proposed in the underlying application.

7. In case the applicant overcomes above mentioned objections with regard to novelty, clarity and support, the present application would therefore satisfy the criterion set forth in **Article 33(3) PCT** and the subject-matter of **claims 1, 2, 6, 7** and **10 - 14** would involve an inventive step (**Rule 65(1)(2) PCT**).

VIII. Certain Observations (Continuation)

1 The application does not meet the requirements of **Article 6 PCT** because claim 1 is not clear for the following reasons:

1.1 The word "early" is a relative term and therefore unclear and undefined if used in the way as in underlying **claim 1**.

1.2 The term "a transplanted subject who is known not to develop CR" of **claim 1** is formulated as an effect to be achieved and therefore does not meet the requirements of **Article 6 PCT** in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. Furthermore, the "at least one gene" in **claim 1** is not further specified. Identifying said "at least one gene" though would be an undue burden for the skilled in the art, **Article 6 PCT**. The **IPEA** doubts, that **any one gene** from a tissue biopsy of a transplanted subject who is known not to develop CR is already an indicator for predicting / early diagnosing chronic rejection (CR), in this respect care also for **claim 2**, bearing said same deficiency. The applicant is reminded to include the essential technical features into the independent claims, which in the present case means the reference to the particular marker gene(s) and their relationship in chronic rejection (CR). For these reasons **claim 1** lacks clarity according to **Art. 6 PCT** taken in combination with **Rule**

6.3 (b) PCT (see also **PCT Preliminary Examination Guidelines III.4.3).**